Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Science of the Total Environment 838 (2022) 155916

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Impact of COVID- 19 pandemic on antidepressants consumptions by wastewater analysis in Turkey

Evsen Yavuz-Guzel [a], Aslı Atasoy [b], İsmail Ethem Gören [c], Nebile Daglioglu [c,*]

[a] Cukurova University, Faculty of Fisheries, Department of Basic Sciences, 01330 Adana, Turkey
[b] Cukurova University, Institute of Addiction and Forensic Sciences, 01330 Adana, Turkey
[c] Cukurova University, Faculty of Medicine, Department of Forensic Medicine, 01330 Adana, Turkey

HIGHLIGHTS

- This study revealed the use of the antidepressant in 10.6 million people.
- Antidepressant use increased during the COVID-19 pandemic.
- The highest increase was detected in venlafaxine.

GRAPHICAL ABSTRACT

ARTICLE INFO

Editor: Kevin V. Thomas

Keywords:
Wastewater-based epidemiology (WBE)
COVID-19
Antidepressants
Drug consumption rate changes

ABSTRACT

The COVID-19 pandemic has been a major challenge worldwide, forcing countries to take restrictive measures beyond conventional methods in their fight against the spread of the disease. Followingly, many studies have been conducted on the effects of these measures on mental health. Wastewater-based epidemiology (WBE) was used in this study to monitor and estimate changes in antidepressant use under normal conditions (2019) and COVID-19 pandemic conditions (2020). Likewise, this study utilized wastewater-based epidemiology (WBE) to monitor and assess changing trends from the pre-pandemic period (2019) to COVID-19 pandemic conditions in antidepressant use (2020). Wastewater samples were collected from 11 cities in Turkey throughout six sampling periods covering the pre-pandemic and during-pandemic periods (June 2019–December 2020). Then, samples were analyzed via LC-MS/MS method. As a result, we observed that venlafaxine was the drug with the highest concentration (mean ± SD: 103.6 ± 112.1 mg/1000p/day). Moreover, city number 6 presented the highest venlafaxine use and the most dramatic increase during the pandemic period. Finally, this study revealed the potential of WBE to estimate the changing trends in mental health during the ongoing pandemic.

1. Introduction

The COVID-19 outbreak, declared a pandemic as of March 2020, has been one of the greatest challenges worldwide. Following the report of the first COVID-19 case in Turkey on 11 March 2020, immediate restrictions were applied on 16 March 2020, and the first partial shutdown was implemented on 14 April (Özdin and Bayrak Özdin, 2020). Since then, there has been a particular interest in investigating the current pandemic's impact on people's mental health. A common consensus of these studies is that the unprecedented end date of the epidemic, uncertainties in treatment methods, forced physical distance, reduction of physical activity, self-isolation, rigid lifestyle changes, and lockdowns which are relatively

* Corresponding author.
E-mail addresses: evsen_yavuz_112@hotmail.com (E. Yavuz-Guzel), asliatsy@gmail.com (A. Atasoy), ismailethemgoren@gmail.com (İ.E. Gören), nebiled@hotmail.com (N. Daglioglu).

http://dx.doi.org/10.1016/j.scitotenv.2022.155916
Received 22 February 2022; Received in revised form 9 May 2022; Accepted 9 May 2022
Available online 12 May 2022

unaccustomed to the modern societies, are among the leading causes underlying mental health problems (Kazan Kızılkurt et al., 2021). Therefore, the pandemic has resulted in higher rates of acute psychological distress, anxiety, insomnia, depression and post-traumatic stress disorder, and addiction problems, including increased alcohol consumption in the general population (Calina et al., 2021; Lei et al., 2020; Liu et al., 2020; Melchor-Martínez et al., 2021; Özdin and Bayrak Özdin, 2020; Xiong et al., 2020). According to the survey results conducted in April 2020 in Turkey, the prevalence of depression and anxiety relatively increased during the pandemic (23.6% and 45.1%, respectively), which was expected considering the psychological effects of the pandemic (Özdin and Bayrak Özdin, 2020). Additionally, the major health problems that preceded COVID-19 have continued to exist, and in many cases, they were exacerbated by the pandemic worldwide (Calina et al., 2021).

Psychological disorders such as depression are associated with deficiencies in one or more monoamines (dopamine, serotonin, and noradrenaline). In the treatment of depression, pharmacological and non-pharmacological principles are commonly available; however, pharmacological therapies, particularly for moderate and severe depression, are the first choice as they are deemed more effective. Antidepressant drugs show their effects by affecting different neurotransmitters responsible for regulating mood. These drugs are classified based on their chemical structure or mechanism of influence (Boogaerts et al., 2019). Currently available medications include serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOs), and benzodiazepines. Generally, such drugs are suggested to be used for a period of time (4–6 months) as a preventive measure against the recurrence of depression (Jjemba, 2008).

Wastewater Based Epidemiology (WBE) is a well-established method that provides information on human consumption and chemical residues of substances such as drugs, food, beverages, tobacco, illicit drugs, pesticides, personal hygiene products, and pollutants at the community level (Gracia-Lor et al., 2017; Reinstadler et al., 2021; van Nuijs et al., 2011; van Wel et al., 2016; Zuccato et al., 2008). Likewise, WBE is a practice that has been successful in examining spatial and temporal trends in substance use (Daglioglu et al., 2017, 2021; Guzel et al., 2020; Melchor-Martínez et al., 2021; Thomas et al., 2012). During the COVID-19 pandemic, numerous studies have been conducted using WBE to detect the SARS-CoV-2 virus in wastewater. Others also utilized WBE to identify changes in the use of legal and illegal substances (Ahmed et al., 2020; Been et al., 2021; EMCDDA, 2021; Galani et al., 2021; Melchor-Martínez et al., 2021; Nason et al., 2021; Wurtzeret al, 2020).

Similarly, we used the WBE method, which provides non-invasive, objective, and real-time unbiased epidemiological information, to monitor and estimate changes in the antidepressant use during the pre-pandemic period, i.e., under normal conditions (2019) and during the COVID-19 pandemic period (2020), i.e., under the extraordinary conditions. Therefore, the study aimed to determine the variation in antidepressant consumptions before and during the pandemic in Turkey. These drugs included a number of antidepressants used to treat anxiety and major depression, including citalopram from the SSRI group, venlafaxine from the SNRI group, opipramol, amitriptyline, imipramine, clomipramine and mirtazapine from the TCA group and moclobemide from the MAOI group. Therefore, antidepressant drugs were analyzed with the LC-MS/MS method in wastewater samples collected from 18 wastewater treatment plants in 11 cities of Turkey during the sampling period.

2. Material and methods

2.1. Selection of targeted compounds

The study consisted of the analysis of antidepressant consumption markers. The targeted compounds were summarized in Table 1.

Table 1
Correction factors and excretion rates used to calculate antidepressant consumption.

Compound	Biomarker for	Excreted unchanged ($\%R_{excreted}$)	Correction Factor (CF)
Moclobemide	Moclobemide	1[a]	100
Mirtazapine	Mirtazapine	4[b]	25
Opipramol	Opipramol	10[c]	10
Venlafaxine	Venlafaxine	4.7[d]	21
Citalopram	Citalopram	20[e]	5
Amitriptyline	Amitriptyline	1[f]	100
Imipramine	Imipramine	5[g]	20
Clomipramine	Clomipramine	1[h]	100

[a] (Bonnet, 2002; Fleishaker et al., 2001; Jauch et al., 1990).
[b] (Brockmöller et al., 2007; de Santana et al., 2008; Timmer et al., 2000).
[c] (Mohopatra et al., 2013).
[d] (Holliday and Benfield, 1995; Kandasamy et al., 2010; Troy et al., 1994).
[e] (Giebułtowicz and Nałecz-Jawecki, 2014; Pollock, 2001; Silva et al., 2012).
[f] (Balant-Gorgia et al., 1982; Breyer-Pfaff, 2004; Breyer-Pfaff et al., 1992; Dahl-Puustinen et al., 1989).
[g] (Bickel and Minder, 1970; Ramey et al., 2014; Sallee and Pollock, 1990).
[h] (Faigle and Dieterle, 1973; Kelly and Myers, 1990; McTavish and Benfield, 1990).

2.2. Target residues and correction factors for back-calculation of drug use

One of the factors affecting the reliability of the back-calculation is the accuracy of the Correction Factors (CF). Zuccato et al. suggested using a specific CF calculated from the percentages of excretion of six different drugs or their metabolites (cocaine, heroin, amphetamine, methamphetamine, ecstasy, and cannabis) (Zuccato et al., 2008). Therefore, the following equation was proposed and applied to obtain the CF (Eq. (1)):

$$CF = \frac{Mw\ (Parent\ Drug)/Mw\ (DTR)}{\%excreted\ as\ DTR} \quad (1)$$

*DTR: Drug target residues, *Mw: Molecular weight.

Following this equation, the CF values of the antidepressants screened in the study were determined and used to calculate retrospective consumption. The CFs of the related substances were presented in Table 1.

2.3. Chemicals and reagents

Reference standards of the targeted compounds and the corresponding isotopically labeled internal standards were obtained from sigma Aldrich, Cerilliant (round rock, TX, USA). Water and methanol of HPLC grade were purchased from Merck (Darmstadt, Germany). Stock solutions of standards were prepared in methanol and stored at -20 °C. calibrators and internal standards were prepared daily

2.4. Sample collection

Wastewater samples were collected from 18 wastewater treatment plants located in 11 different cities in Turkey (Table S1). 24-h composite wastewater samples from WWTPs were collected every three months for seven consecutive days, in 6 periods in total, from June 2019 to December 2020 (25 June-1 July 2019; 24–30 September 2019; 17–23 December 2019; 30 June- 7 July 2020; 29 September- 6 October 2020; 15–22 December 2020). However, we could not collect wastewater samples in March 2020, the onset of the pandemic, due to restrictions enforced by the Ministry of Environment, Urbanization, and Climate Change of the Turkish Republic.

As stated earlier, the study concerns changes in trends in the use of antidepressants during the pre-pandemic and the COVID-19 pandemic period. Therefore, to compare the two periods, we defined the interval from June 2019 to December 2019 as “normal conditions”, and the interval from June 2020 to December 2020 as “COVID-19 pandemic conditions”.

2.5. Sample preparation and instrumental analysis

The method used in our previous studies was used as the extraction method (Daglioglu et al., 2021). Initially, water samples were prefiltered through a 0.7 μm glass fiber filter (Merck Millipore, Cork, IRL) followed by solid extraction (SPE). SPE cartridges (Oasis HLB, 60 mg/3 cc, Waters, Milford, MA, USA) were then preconditioned with 3 mL of methanol and 3 mL of ultrapure water. Water samples (50 mL) were passed through SPE cartridges, rinsed with 3 mL ultrapure water, and dried for 10 min. Then, the SPE cartridges were eluted with methanol (twice with 3 mL). Extracts were evaporated to dryness under N2 (Teknosem, TAB-40 WEL, Istanbul, Turkey), and the residue was reconstituted in 500 μL of methanol and transferred to amber glass bottles.

Samples were analyzed using a Shimadzu 8040 liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Kyoto, Japan). The chromatographic separation of analytes was performed using a pentafluorophenyl propyl (PFPP) column (Allure 50 × 2.1 mm i.d., 5 μm, Restek, Bellefonte, PA, USA), maintained at 40 °C. Gradient elution was performed at a flow rate of 0.4 mL/min, using 10 mM ammonium formate in water (A) and methanol (B), changing as follows: 10% B at 0.1 min, 90% B at 10.0 min, 10% B at 15.0 min, with a total run time of 18 min. The injection volume was 10 μL. Detection and quantification were performed by integrating the area under the specific multiple reaction monitoring (MRM) chromatograms in reference to the integrated area of the internal standard (IS-diazepam-d5) with electrospray ionization source operating in positive mode. The analytical LC-MS/MS parameters and operating conditions for the analytes are shown in Table S2.

2.6. Quality assurance/quality control

An 8-point calibration series was used to quantify antidepressant drugs for the method validation. The calibration ranges were 1–500 ng/L. It was evaluated through the calibration curves by linear regression analysis calculated by the least-squares with a weighting factor of $1/x^2$, and it was expressed by the coefficient of determination (r^2). The method's sensitivity for each matrix was assessed by determining the LODs and LLOQs from the corresponding calibration plot as the signal to noise ratios of 3:1 and 10:1, respectively. Lower limits of quantification (LOQs) range of 0.93 to 1.0 ng/L for all compounds.

To determine the extraction efficiency, accuracy, precision, and matrix effect studies, quality-control water samples were conducted at different concentration levels for each analyte by spiking into blank water samples. Analyses at each concentration level were repeated six times. Obtained results of non-spiked water samples were substracted before recovery (Rec) calculations. The standard deviation (SD), relative standard deviation (RSD), and Rec repeatability values were calculated. Rec values for the all analytes was among average 85%–%115 range with a precision (%RSD) below 15%. All extractions were performed along with daily prepared ILIS-added blank water samples, and methanol was injected before each sequence as a check for carry-over. In addition, after every 20 samples, internal quality control samples (spiked with 5, 20, 250, and 450 ng/L for antidepressant drugs) were analyzed. No marked carry-over was observed for all of the analytes.

2.7. Estimation of loads and consumption rates

Daily mass loads of biomarkers were calculated by multiplying their concentrations in the 24-h composite samples by the corresponding daily flows of wastewater. Mass loads were then normalized to the number of people served by the WWTP to yield the consumptions (mg/1000p/day).

Consumed quantities and per capita intakes were estimated for antidepressants using the following Eq. (2):

$$\text{CONSUMPTION} = \text{Conc.} \times \text{F} \times \text{CF} \times \text{P}^{-1} \quad (2)$$

Conc. is the concentration of each target analyte (ng/L) in influent wastewater, F is the daily wastewater flow rate (m^3/day), CF is the specific correction factor for each analyte (Table 1), and P is the population served by the WWTP.

The defined daily dose (DDD) per 1000 people for all antidepressants was calculated according to World Health Organization Collaborating Centre for Drug Statistics Methodology (World Health Organization, 2018). The calculated DDDs for the antidepressants were shown in Table S3.

2.8. Statistical methods

All statistics were performed by IBM SPSS software v24. Descriptive statistics (mean and standard deviation) were used to characterize population normalized loads of the measured drugs. Mann-Whitney U, one-way ANOVA, and Kruskal-Wallis tests were computed to compare the measurements of the groups. Linear regression analysis was performed to determine the relationship between the estimated SUM of antidepressant consumptions and the number of daily cases in Turkey during the COVID-19 pandemic. Multiple group variability was evaluated statistically by two-way ANOVA. Statistical significance was set at $p < 0.05$.

3. Results and discussion

3.1. Monitoring wastewater before and after the COVID-19 pandemic

This study presents baseline monitoring data to evaluate the impact of the COVID-19 pandemic on antidepressant drug use in 11 cities in Turkey. As a result, considering the analysis of studied antidepressants, the drug with the highest consumption was venlafaxine (mean ± SD: 103.6 ± 112.1 mg/1000p/day), followed by amitriptyline, clomipramine, citalopram, moclobemide, and mirtazapine, respectively (Fig. 1). Meanwhile, opipramol and imipramine were found in lower concentrations than other drugs. Moreover, similar to mg/1000p/day values, the highest consumption amount was observed in venlafaxine according to DDDs calculations in Table S3, followed by citalopram, amitriptyline, mirtazapine, clomipramine, and moclobemide, respectively. Similarly, the lowest consumption based on DDDs was observed in opipramil and imipramine. Also, the average mass loads observed in both periods varied greatly, as evident in the relative standard deviations (RSD). For instance, the RSD values for venlafaxine and opipramol were 108.2% and 69.3%, respectively. The variation in RSD values was due to concentration differences among cities as well as due to daily, weekly, and temporal changes.

Additionally, there was no statistically significant difference in weekly and daily use of all drugs in both periods ($p > 0.05$) (Fig. 2). Likewise, in their WBE study conducted between 2016 and 2020 in Innsbruck, Belgium, Reinstadler et al. observed no statistically significant difference in venlafaxine consumption amount before and after the pandemic and between weekends and weekdays (Reinstadler et al., 2021). However, when the effect of pandemic quarantine on the amount of selected antidepressant use was evaluated, the figure for the studied antidepressants was found to

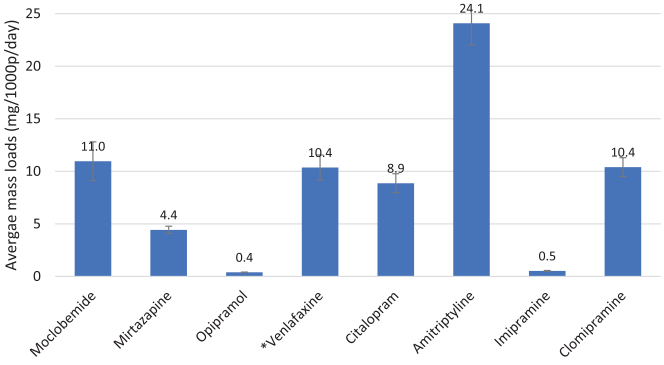

Fig. 1. Average consumptions observed for 8 targeted compounds during normal conditions (2019) and COVID-19 pandemic conditions (2020) (*the venlafaxine results were reduced 10 times to facilitate comparison).

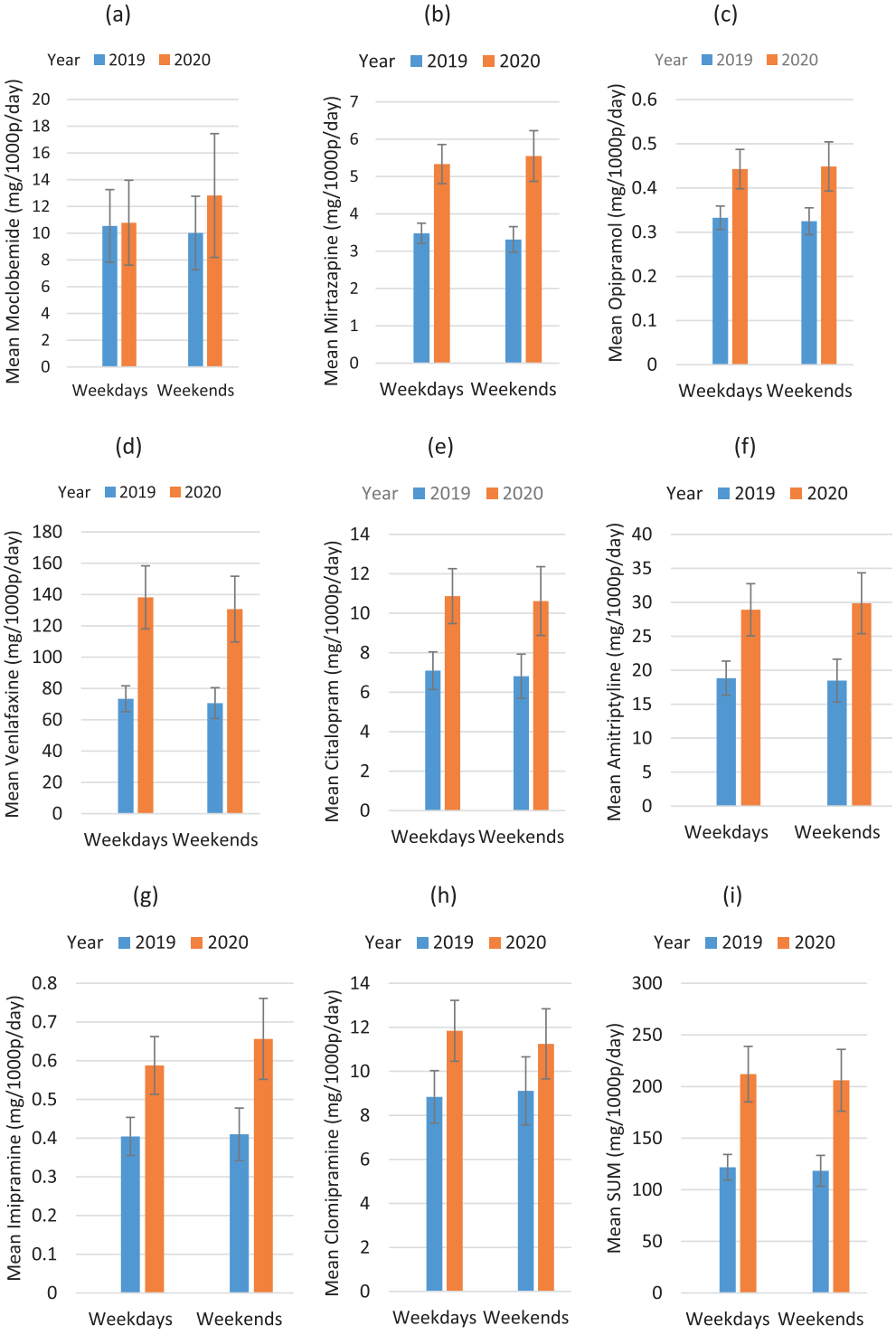

Fig. 2. Weekly variations of all antidepressant consumptions between normal and pandemic periods.

have increased significantly during the quarantine period, except for moclobemide and clomipramine (Table 2) (Fig. 3). Comparably, a significant increase was observed in the sum of antidepressant drug consumption during the pandemic period ($p < 0.001$). Finally, linear regression analysis was performed to determine the relationship between the sum of estimated daily antidepressant use during the Covid period and the number of daily cases in Turkey (Fig. S1). The results showed that daily antidepressant consumption increased in correlation to the increase in COVID-19 cases ($r^2 = 0.705$).

3.2. Prevalence of mental health disorders and antidepressant consumption

The current study's findings show that antidepressant usage increased during the pandemic in Turkey (Table 2). The common practice of monitoring antidepressant use is generally based on population surveys, prescription, and sales data. For instance, it was reported that there was a 68% increase in antidepressant drug sales at the onset of the pandemic (March 2020) in Australia (Tscharke et al., 2021). However, no such data is available for Turkey. Also, the participants in these surveys are likely to not

Table 2
Average antidepressants consumption during normal conditions (2019) and COVID-19 pandemic conditions (2020).

Drugs	Year		*p*-value
	2019 Consumption Mean ± SD (mg/1000p/day)	2020 Consumption Mean ± SD (mg/1000p/day)	
Moclobemide	10.3 ± 15.7	11.7 ± 21.0	0.170
Mirtazapine	3.4 ± 2.0	5.43 ± 3.99	<0.050
Opipramol	0.33 ± 1.7	0.45 ± 0.33	<0.050
Venlafaxine	72.2 ± 60.6	135 ± 140	<0.050
Citalopram	6.97 ± 6.94	10.8 ± 10.4	<0.050
Amitriptyline	18.7 ± 18.5	29.3 ± 27.8	<0.050
Imipramine	0.41 ± 0.32	0.62 ± 0.54	<0.050
Clomipramine	8.96 ± 7.97	11.6 ± 9.76	0.055
SUM (Total)	120 ± 92.6	209 ± 193	<0.050

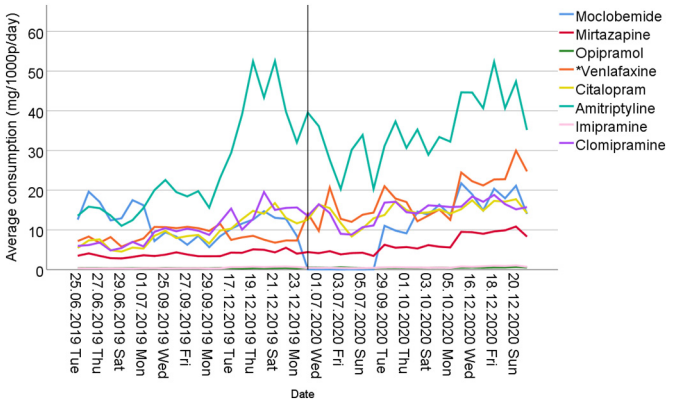

Fig. 3. Temporal patterns in average consumptions for all drugs between normal conditions (2019) and COVID-19 pandemic conditions (2020) (**the venlafaxine results were reduced 10 times to facilitate comparison*).

report drug use for fear of being stigmatized. In addition, due to demanding challenges in processing the data on drug sales in Turkey, it is not possible to keep records of figures. This issue was further realized in the survey study, in which the current prevalence of depressive disorder was estimated in 27 European countries, as it was reported that the data obtained from Turkey were not of satisfactory quality and therefore excluded from the study (Arias-de la Torre et al., 2021).

There are few studies evaluating the impact of the COVID-19 pandemic on mental health in Turkey (Kazan Kızılkurt et al., 2021; Özdin and Bayrak Özdin, 2020). Kazan Kızılkurt et al. found that people mostly were in an anxious mood mainly due to two main factors; increased use of social media and increased time spent on the news about the pandemic (Kazan Kızılkurt et al., 2021). However, in contrast to current study, these studies mentioned above did not provide any data on antidepressants use. Therefore, concerning issues with survey studies and lacks of monitoring data in others, WBE method is of paramount importance particularly tracing markers of changing trends in antidepressants use and providing monitoring data.

3.3. Comparison of WBE results with other countries

In this study, the mean amount of citalopram was found to be 8.87 ± 9.05 mg/1000 p/day. Since no study has reported the WBE estimated antidepressant use method in terms of DDD unit so far, the consumption figures of other countries were compared in mg/1000p/day. For instance, Riva et al. (Riva et al., 2020) estimated the daily dose to be approximately 18.8 ± 5.9 mg/1000p/day based on a wastewater sample analysis of 6 cities in Italy in 2017. The reported mean amount of citalopram was higher than the amount observed in our study.

The mean values of moclobemide, mirtazapine, opipramol, amitriptyline, imipramine, and clomipramine consumptions were estimated as 10.96 ± 18.45, 4.43 ± 3.33, 0.39 ± 0.27, 24.09 ± 24.28, 0.52 ± 0.47 and 10.40 ± 9.04 mg/1000p/day, respectively. There is a limited number of studies on monitoring antidepressants in wastewater in the literature. Among a limited number of studies, one particular study consisting of wastewater treatment plants in 4 Belgium cities investigated all similar antidepressants identified in the current one. As a result, Boogaerts et al. reported that the consumption amount of amitriptyline (15.1 ± 4.12 mg/1000p/day), citalopram (1.28 ± 0.361 mg/1000p/day), and clomipramine (1.17 ± 0.237 mg/1000p/day). These values were much lower than the ones observed in the current study. Nonetheless, both studies detected the same levels of moclobemide (8.43 ± 4.44 mg/1000p/day), while the mean amount of mirtazapine (17.3 ± 3.64 mg/1000p/day) was higher in the first study. Finally, opipramol and imipramine were also analyzed; however, they could not be detected (Boogaerts et al., 2019).

The mean venlafaxine use detected in this study was 103.6 ± 112.1 mg/1000p/day. Reinstadler et al. estimated the mean amount of venlafaxine consumed as 106.2 ± 24.1 mg/1000p/day in their WBE-based study (Reinstadler et al., 2021). Likewise, these results were similar to the ones observed in our study. Finally, the study by Boogaerts et al. estimated a higher amount of venlafaxine than the value observed in the current study (174.7 ± 42.98 mg/1000p/day) (Boogaerts et al., 2019).

3.4. Spatial variation

This study estimated the mean amount of SUM of the antidepressant use as 165.0 ± 157.6 mg/1000p/day. Moreover, examining the cities included in the study noted that the highest usage rate and increase during the covid period were in City 6, followed by City 8, City 1, and City 2 (Fig. 4). While the use of antidepressants in City 10 decreased during the covid period, the lowest increases were in City 11, City 9, and City 3, respectively. Also, the total SUM detected in City 6, City 8, City 1, City 5, and City 7, respectively, was higher than the average amount of antidepressant use in Turkey. Finally, in order, the lowest amounts were found in City 11, City 3, City 9, City 2, City 10, and City 4.

Venlafaxine and citalopram consumption increased during the pandemic period in all cities except City 10 and City 11 (Table S4). Moreover, amitriptyline consumption increased during the pandemic period in all regions. In City 11, moclobemide consumption could not be detected in both periods, while opipramol consumption was observed only in the pandemic period. Finally, clomipramine consumption significantly increased in cities 3 and 6 during the pandemic ($p < 0.05$).

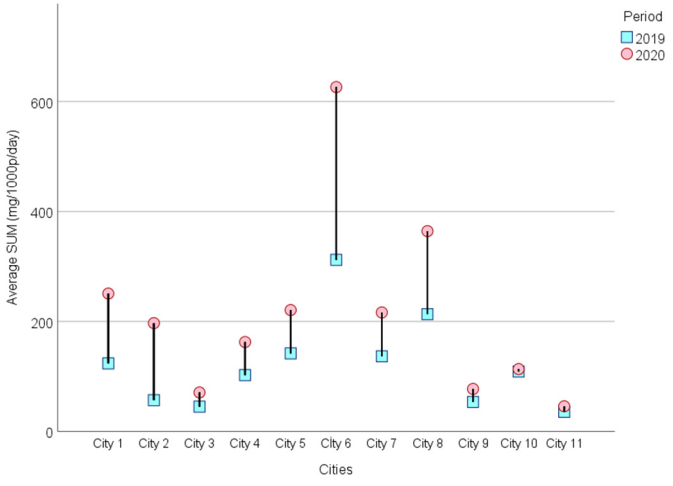

Fig. 4. Drop-line graph for average consumptions (mg/1000p/day) of total antidepressant (SUM) in 11 cities in Turkey by study periods.

This WBE-based approach data showed that long-term antidepressant drug use in the treatment of depression increased during the quarantine period compared to the previous period in Turkey. Additionally, results indicated that the COVID-19 pandemic negatively affected mental health in Turkey in general.

3.5. Limitations and uncertainties of the study

Currently, monitoring of antidepressant use relies heavily on general population surveys, prescriptions, and sales data. These approaches provide relevant information about well-being patterns and medical use in a general population. However, WBE has proven its potential to predict near real-time drug consumption. Nevertheless, WBE studies have particular uncertainties and limitations regarding sample collection, the extraction process, the stability of substances in wastewater, and limitations in back calculations due to difficulties determining population size (Melchor-Martínez et al., 2021). On the other hand, variations in real-time population estimation and issues with instrumental analysis (i.e., calibration errors in flowmeter measurements) were the standard limitations and uncertainties for antidepressant biomarkers. These limitations are likely to affect per capita antidepressants consumption calculations. Moreover, a further issue was that some antidepressants are used as pain killers. Despite its limitations and uncertainties, WBE has an essential role in profiling drug consumption in real time, where traditional methods are unavailable to monitor changing trends.

In addition, we could not examine the metabolites of the antidepressant drugs screened in the study since there are no reference standards for validation. Consequently, CF was used on the parent substance in back calculations to investigate the consumption rate. Therefore, we aim to monitor more cities in Turkey and with different antidepressant and their metabolites included in future studies.

4. Conclusions

This study showed that antidepressant consumptions increased in 11 cities in Turkey during the COVID-19 pandemic. The highest consumption was detected in venlafaxine, followed by amitriptyline, clomipramine, citalopram, moclobemide, and mirtazapine, respectively. Additionally, results showed that daily antidepressant consumption increased in correlation to the increase in COVID-19 cases.

Limited data are available on monitoring the change in antidepressant consumption before and during the COVID-19 pandemic. While more research is needed to understand these changing trends, the findings of this study can help authorities take action in health and public services to prepare for the future challenges of the ongoing pandemic.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.155916.

CRediT authorship contribution statement

Evsen Yavuz Guzel and Aslı Atasoy carried out the experiments and verified the analytical methods. Nebile Daglioglu supervised the findings of this work and developed the theory. Ismail Ethem Goren wrote the manuscript with support from Nebile Daglioglu.

Funding

None of funding.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

All the authors would like to thank the administrators of eighteen WWTPs in eleven countries of Turkey for their help in the sampling of influent wastewaters from WWTPs.

References

Ahmed, W., Angel, N., Edson, J., Bibby, K., Bivins, A., O'Brien, J.W., Choi, P.M., Kitajima, M., Simpson, S.L., Li, J., Tscharke, B., Verhagen, R., Smith, W.J.M., Zaugg, J., Dierens, L., Hugenholtz, P., Thomas, K.V., Mueller, J.F., 2020. First confirmed detection of SARS-CoV-2 in untreated wastewater in Australia: a proof of concept for the wastewater surveillance of COVID-19 in the community. Sci. Total Environ. 728, 138764. https://doi.org/10.1016/j.scitotenv.2020.138764.

Arias-de la Torre, J., Vilagut, G., Ronaldson, A., Serrano-Blanco, A., Martín, V., Peters, M., Valderas, J.M., Dregan, A., Alonso, J., 2021. Prevalence and variability of current depressive disorder in 27 European countries: a population-based study. Lancet Public Health 6, e729–e738. https://doi.org/10.1016/S2468-2667(21)00047-5.

Balant-Gorgia, A.E., Schulz, P., Dayer, L., Balant, L., Kubli, A., Gertsch, C., Garrone, G., 1982. Role of oxidation polymorphism on blood and urine concentrations of amitriptyline and its metabolites in man. Arch. Psychiatr. Nervenkr. 232, 215–222. https://doi.org/10.1007/BF02141782.

Been, F., Emke, E., Matias, J., Baz-lomba, J.A., Castiglioni, S., Campos-mañas, M., Celma, A., Voogt, P.De, Hernández, F., Kasprzyk-hordern, B., Reid, M., Salgueiro-González, N., Steenbeek, R., Nuijs, A.L.N.Van, Zuccato, E., Bijlsma, L., 2021. Changes in drug use in European cities during early COVID-19 lockdowns - a snapshot from wastewater analysis. Environ. Int. 153, 106540. https://doi.org/10.1016/j.envint.2021.106540.

Bickel, M.H., Minder, R., 1970. Metabolism and biliary excretion of the lipophilic drug molecules, imipramine and desmethylimipramine in the rat-II.Uptake into bile micelles. Biochem. Pharmacol. 19, 2437–2443. https://doi.org/10.1016/0006-2952(70)90268-6.

Bonnet, U., 2002. Moclobemide: evolution, pharmacodynamic, and pharmacokinetic properties. CNS Drug Rev. 8, 283–308. https://doi.org/10.1111/j.1527-3458.2002.tb00229.x.

Boogaerts, T., Degreef, M., Covaci, A., van Nuijs, A.L.N., 2019. Development and validation of an analytical procedure to detect spatio-temporal differences in antidepressant use through a wastewater-based approach. Talanta 200, 340–349. https://doi.org/10.1016/j.talanta.2019.03.052.

Breyer-Pfaff, U., 2004. The metabolic fate of amitriptyline, nortriptyline and amitriptylinoxide in man. Drug Metab. Rev. 36, 723–746. https://doi.org/10.1081/DMR-200033482.

Breyer-Pfaff, U., Pfandl, B., Nill, K., Nusser, E., Monney, C., Jonzier-Perey, M., Baettig, D., Baumann, P., 1992. Enantioselective amitriptyline metabolism in patients phenotyped for two cytochrome P450 isozymes. Clin. Pharmacol. Ther. 52, 350–358. https://doi.org/10.1038/clpt.1992.155.

Brockmöller, J., Meineke, I., Kirchheiner, J., 2007. Pharmacokinetics of mirtazapine: enantioselective effects of the CYP2D6 ultra rapid metabolizer genotype and correlation with adverse effects. Clin. Pharmacol. Ther. 81, 699–707. https://doi.org/10.1038/sj.clpt.6100116.

Calina, D., Hartung, T., Mardare, I., Mitroi, M., Poulas, K., Tsatsakis, A., Rogoveanu, I., Docea, A.O., 2021. COVID-19 pandemic and alcohol consumption: impacts and interconnections. Toxicol. Rep. 8, 529–535. https://doi.org/10.1016/j.toxrep.2021.03.005.

Daglioglu, N., Kilercioglu, S., Guzel, E.Y., 2017. Determination of illicit drugs in sewage treatment plants in Adana, Turkey. SETAC Europe 27th Annual Meeting, p. 309 Brussels, Belgium.

Daglioglu, N., Guzel, E.Y., Atasoy, A., Gören, İ.E., 2021. Comparison of community illicit drug use in 11 cities of Turkey through wastewater-based epidemiology. Environ. Sci. Pollut. Res. 28, 15076–15089. https://doi.org/10.1007/s11356-020-11404-9.

Dahl-Puustinen, M.-L., Åberg-Wistedt, A., Bertilsson, L., 1989. Glucuronidation of amitriptyline in man in vivo. Pharmacol. Toxicol. 65, 37–39. https://doi.org/10.1111/j.1600-0773.1989.tb01123.x.

EMCDDA, 2021. Impact of COVID-19 on Drug Markets, Use, Harms and Drug Services in the Community and Prisons: Results From an EMCDDA Trendspotter Study. Publications Office of the European Union https://doi.org/10.2810/222454.

Faigle, J.W., Dieterle, W., 1973. The metabolism and pharmacokinetics of clomipramine (Anafranil). J. Int. Med. Res. 1, 281–290. https://doi.org/10.1177/030006057300100502.

Fleishaker, J.C., Ryan, K.K., Jansat, J.M., Carel, B.J., Bell, D.J.A., Burke, M.T., Azie, N.E., 2001. Effect of MAO-A inhibition on the pharmacokinetics of almotriptan, an antimigraine agent in humans. Br. J. Clin. Pharmacol. 51, 437–441. https://doi.org/10.1046/j.1365-2125.2001.01367.x.

Galani, A., Alygizakis, N., Aalizadeh, R., Kastritis, E., Dimopoulos, M., Thomaidis, N.S., 2021. Patterns of pharmaceuticals use during the first wave of COVID-19 pandemic in Athens, Greece as revealed by wastewater-based epidemiology. Sci. Total Environ. 798, 149014. https://doi.org/10.1016/j.scitotenv.2021.149014.

Giebułtowicz, J., Nałecz-Jawecki, G., 2014. Occurrence of antidepressant residues in the sewage-impacted Vistula and Utrata rivers and in tap water in Warsaw (Poland). Ecotoxicol. Environ. Saf. 104, 103–109. https://doi.org/10.1016/j.ecoenv.2014.02.020.

Gracia-Lor, E., Castiglioni, S., Bade, R., Been, F., Castrignanò, E., Covaci, A., González-Mariño, I., Hapeshi, E., Kasprzyk-Hordern, B., Kinyua, J., Lai, F.Y., Letzel, T., Lopardo, L., Meyer, M.R., O'Brien, J., Ramin, P., Rousis, N.I., Rydevik, A., Ryu, Y., Santos, M.M., Senta, I., Thomaidis, N.S., Veloutsou, S., Yang, Z., Zuccato, E., Bijlsma, L., 2017. Measuring biomarkers in wastewater as a new source of epidemiological information: current state and future perspectives. Environ. Int. 99, 131–150. https://doi.org/10.1016/j.envint.2016.12.016.

Guzel, E.Y., Atasoy, A., Gören, İ.E., Daglioglu, N., 2020. Estimation of alcohol and nicotine consumption in 11 cities of Turkey using wastewater-based epidemiology. Drug Test. Anal. https://doi.org/10.1002/dta.2979.

Holliday, S.M., Benfield, P., 1995. Venlafaxine. Drugs 49, 280–294. https://doi.org/10.2165/00003495-199549020-00010.

Jauch, R., Griesser, E., Oesterhelt, G., Arnold, W., Melster, W., Ziegler, W.H., Guentert, T.W., 1990. Biotransformation of moclobemide in humans. Acta Psychiatr. Scand. 82, 87–90. https://doi.org/10.1111/j.1600-0447.1990.tb05344.x.

Jjemba, P.K., 2008. Pharma-ecology: The Occurrence and Fate of Pharmaceuticals and Personal Care Products in the Environment. John Wiley & Sons Inc, Hoboken, NJ, USA https://doi.org/10.1002/9780470369340.

Kandasamy, M., Srinivas, P., Subramaniam, K., Ravi, S., John, J., Shekar, R., Srinivas, N., Thangam, S., 2010. Differential outcomes from metabolic ratios in the identification of CYP2D6 phenotypes-focus on venlafaxine and O-desmethylvenlafaxine. Eur. J. Clin. Pharmacol. 66, 879–887. https://doi.org/10.1007/s00228-010-0829-y.

Kazan Kızılkurt, O., Yılmaz, A., Noyan, C.O., Dilbaz, N., 2021. Health anxiety during the early phases of COVID-19 pandemic in Turkey and its relationship with postpandemic attitudes, hopelessness, and psychological resilience. Perspect. Psychiatr. Care 57, 399–407. https://doi.org/10.1111/ppc.12646.

Kelly, M.W., Myers, C.W., 1990. Clomipramine: a tricyclic antidepressant effective in obsessive compulsive disorder. DICP 24, 739–744. https://doi.org/10.1177/106002809002400718.

Lei, L., Huang, X., Zhang, S., Yang, J., Yang, L., Xu, M., 2020. Comparison of prevalence and associated factors of anxiety and depression among people affected by versus people unaffected by quarantine during the COVID-19 epidemic in southwestern China. Med. Sci. Monit. 26, 1–12. https://doi.org/10.12659/MSM.924609.

Liu, C.H., Zhang, E., Tin Fifi Wong, G., Hyun, S., Hahm, H., 2020. Factors associated with depression, anxiety, and PTSD symptomatology during the COVID-19 pandemic: clinical implications for U.S. young adult mental health. Psychiatry Res. 290, 113172. https://doi.org/10.1016/j.psychres.2020.113172.

McTavish, D., Benfield, P., 1990. Clomipramine. An overview of its pharmacological properties and a review of its therapeutic use in obsessive compulsive disorder and panic disorder. Drugs 39, 136–153. https://doi.org/10.2165/00003495-199039010-00010.

Melchor-Martínez, E.M., Jiménez-Rodríguez, M.G., Martínez-Ruiz, M., Peña-Benavides, S.A., Iqbal, H.M.N., Parra-Saldívar, R., Sosa- Hernández, J.E., 2021. Antidepressants surveillance in wastewater: overview extraction and detection. Case Stud. Chem. Environ. Eng. 3, 100074. https://doi.org/10.1016/j.cscee.2020.100074.

Mohopatra, S., Rath, N., Agrawal, A., Verma, J., 2013. Opipramol: a novel drug. Delhi Psyciathry J. 16, 409–411.

Nason, S.L., Lin, E.Z., Eitzer, B.D., Koelmel, J.P., Peccia, J., 2021. Traffic, Drugs, Mental Health, and Disinfectants: Changes in Sewage Sludge Chemical Signatures During a COVID-19 Community Lockdown (preprint). ChemRxiv, pp. 1–24 https://doi.org/10.26434/chemrxiv.13562525.v1.

van Nuijs, A.L.N., Castiglioni, S., Tarcomnicu, I., Postigo, C., de Alda, M.L., Neels, H., Zuccato, E., Barcelo, D., Covaci, A., 2011. Illicit drug consumption estimations derived from wastewater analysis: a critical review. Sci. Total Environ. 409, 3564–3577. https://doi.org/10.1016/j.scitotenv.2010.05.030.

Özdin, S., Bayrak Özdin, Ş., 2020. Levels and predictors of anxiety, depression and health anxiety during COVID-19 pandemic in Turkish society: the importance of gender. Int. J. Soc. Psychiatry 66, 504–511. https://doi.org/10.1177/0020764020927051.

Pollock, B.G., 2001. Citalopram: a comprehensive review. Expert. Opin. Pharmacother. 2, 681–698. https://doi.org/10.1517/14656566.2.4.681.

Ramey, K., Ma, J.D., Best, B.M., Atayee, R.S., Morello, C.M., 2014. Variability in metabolism of imipramine and desipramine using urinary excretion data. J. Anal. Toxicol. 38, 368–374. https://doi.org/10.1093/jat/bku034.

Reinstadler, V., Ausweger, V., Grabher, A.L., Kreidl, M., Huber, S., Grander, J., Haslacher, S., Singer, K., Schlapp-Hackl, M., Sorg, M., Erber, H., Oberacher, H., 2021. Monitoring drug consumption in Innsbruck during coronavirus disease 2019 (COVID-19) lockdown by wastewater analysis. Sci. Total Environ. 757, 144006. https://doi.org/10.1016/j.scitotenv.2020.144006.

Riva, F., Castiglioni, S., Pacciani, C., Zuccato, E., 2020. Testing urban wastewater to assess compliance with prescription data through wastewater-based epidemiology: first case study in Italy. Sci. Total Environ. 739, 139741. https://doi.org/10.1016/j.scitotenv.2020.139741.

Sallee, F.R., Pollock, B.G., 1990. Clinical pharmacokinetics of imipramine and desipramine. Clin. Pharmacokinet. 18, 346–364. https://doi.org/10.2165/00003088-199018050-00002.

de Santana, F.J.M., Lanchote, V.L., Bonato, P.S., 2008. Capillary electrophoretic chiral determination of mirtazapine and its main metabolites in human urine after enzymatic hydrolysis. Electrophoresis 29, 3924–3932. https://doi.org/10.1002/elps.200800053.

Silva, L.J.G., Lino, C.M., Meisel, L.M., Pena, A., 2012. Selective serotonin re-uptake inhibitors (SSRIs) in the aquatic environment: an ecopharmacovigilance approach. Sci. Total Environ. 437, 185–195. https://doi.org/10.1016/j.scitotenv.2012.08.021.

Thomas, K.V., Bijlsma, L., Castiglioni, S., Covaci, A., Emke, E., Grabic, R., Hernández, F., Karolak, S., Kasprzyk-Hordern, B., Lindberg, R.H., Lopez de Alda, M., Meierjohann, A., Ort, C., Pico, Y., Quintana, J.B., Reid, M., Rieckermann, J., Terzic, S., van Nuijs, A.L.N., de Voogt, P., 2012. Comparing illicit drug use in 19 European cities through sewage analysis. Sci. Total Environ. 432, 432–439. https://doi.org/10.1016/j.scitotenv.2012.06.069.

Timmer, C.J., Ad Sitsen, J.M., Delbressine, L.P., 2000. Clinical pharmacokinetics of mirtazapine. Clin. Pharmacokinet. 38, 461–474. https://doi.org/10.2165/00003088-200038060-00001.

Troy, S.M., Schultz, R.W., Parker, V.D., Chiang, S.T., Blum, R.A., Hicks, R., Chiang, T., Douglas, F., Parker, D., 1994. The effect of renal disease on the disposition of venlafaxine. Clin. Pharmacol. Ther. 56, 14–21. https://doi.org/10.1038/clpt.1994.95.

Tscharke, B.J., Hollingworth, S., van Driel, M.L., O'Brien, J.W., Thai, P.K., 2021. The impact of COVID-19 on antidepressant sales and prescription dispensing in Australia. Aust. N. Z. J. Psychiatry 00. https://doi.org/10.1177/00048674211068396 000486742110683.

van Wel, J.H.P., Gracia-Lor, E., van Nuijs, A.L.N., Kinyua, J., Salvatore, S., Castiglioni, S., Bramness, J.G., Covaci, A., Van Hal, G., 2016. Investigation of agreement between wastewater-based epidemiology and survey data on alcohol and nicotine use in a community. Drug Alcohol Depend. 162, 170–175. https://doi.org/10.1016/j.drugalcdep.2016.03.002.

World Health Organization, 2018. WHO Collaborating Centre for Drug Statistics Methodology [WWW Document]. URL https://www.whocc.no/atc/structure_and_principles/.

Wurtzeret al., 2020 S. Wurtzer V. Marechal M. Jm L. Moulin S. Université U.M.R. Metis Z. Atelier 2020. Time course quantitative detection of SARS-CoV-2 in Parisian wastewaters correlates with COVID-19 confirmed cases Eau de Paris , R & D Laboratory , DRDQE 11 Avenue Jean Jaurès 94200 Ivry / Seine , France . Corresponding authors * laurent.moulin@eaudeparis 10–13.

Xiong, J., Lipsitz, O., Nasri, F., Lui, L.M.W., Gill, H., Phan, L., Chen-Li, D., Iacobucci, M., Ho, R., Majeed, A., McIntyre, R.S., 2020. Impact of COVID-19 pandemic on mental health in the general population: a systematic review. J. Affect. Disord. 277, 55–64. https://doi.org/10.1016/j.jad.2020.08.001.

Zuccato, E., Chiabrando, C., Castiglioni, S., Bagnati, R., Fanelli, R., 2008. Estimating community drug abuse by wastewater analysis. Environ. Health Perspect. 116, 1027–1032. https://doi.org/10.1289/ehp.11022.